Effects of measles on the immune response of Nigerian children

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Whittle, H. C., Bradley-Moore, A., Fleming, A., and Greenwood, B. M.
(1973). *Archives of Disease in Childhood*, **48**, 753. **Effects of measles on the**
immune response of Nigerian children. The effects of measles on the immune
system of Nigerian children were investigated. At the time of the rash, skin tests to
tuberculin purified protein derivative, candida, and streptococcal antigens were nega-
tive. Skin sensitization with dinitrochlorobenzene and lymphocyte transformation by
phytohaemagglutinin were normal. Antibody response to the H and O antigens of
Salmonella typhi was deficient. Established humoral response and serum immuno-
globulin levels were normal.

Immunosuppression induced by the measles virus, sometimes acting synergistically
with immunosuppression due to malnutrition, may contribute to the high prevalence of
serious complications seen after measles in tropical developing countries.

Measles is still a major cause of death in children
of the developing countries (Morley, 1969). In
Africa mortality among hospital patients ranges
from 5 to 25%, and prolonged morbidity due to
secondary infection and malnutrition is frequent
(Morley, Woodland, and Martin, 1963; Murphy,
1966). Tuberculosis and moniliasis, infections
normally controlled by cell-mediated immune
responses, are known to follow measles (Bech, 1962;
Smythe *et al.*, 1971). Pyogenic infections, which
are usually limited by humoral immune responses,
are also frequent and severe in children with measles
(Morley, 1969; Taneja, Ghai, and Bhakoo, 1962).

In 1908, von Pirquet showed that the tuberculin
reaction became negative during an attack of measles
and this observation has been confirmed in natural
measles (Starr and Berkovich, 1964) and vaccine-
induced measles (Fireman, Friday, and Kumate,
1969). Lymphocyte transformation on stimulation
with phytohaemagglutinin (PHA) has been reported
to be depressed in natural measles (Kadowaki,
Nihira, and Nakao, 1970) but to be normal in
vaccine-induced measles (Fireman *et al.*, 1969).
Addition of measles virus to lymphocyte cultures
did not suppress the response of the cells to PHA

(Smithwick and Berkovich, 1966), but we have been
unable to find any reports of the effects of measles on
humoral immunity in man.

We have investigated the effects of measles
infection on the immune system of young children
in Nigeria. As immunity is impaired in severe
protein-calorie malnutrition (Geefhuysen *et al.*,
1971; Smythe *et al.*, 1971), we have also studied the
effects of measles on the nutritional state of the
children.

Materials and methods

Patients. 33 children with acute measles, diagnosed
by the presence of Koplik's spots or a typical rash, were
studied as outpatients at the Ahmadu Bello University
Hospital, Zaria, from February to May 1972. Only
patients with a rash less than 4 days old were selected.
Patients with malaria parasitaemia or obvious clinical
signs of malnutrition were excluded. The mean age of
the patients was 31 months (range 7–72 months). 30
patients weighed 80% or more of the Harvard standard
of weight for age (Jelliffe, 1966), 1 patient weighed 75%
of the standard, and the other 2 just under 70%.
Judging by the criteria of Morley, Martin, and Allen
(1967), none of the children had measles severe enough
to warrant hospital admission. Healthy controls were
selected from sibs accompanying patients to hospital.
They matched the patients for age and weight-for-age.

The consent of the parents of each child was obtained before they were included in the study.

Schedule. On day 1 the children were examined, weighed, and blood was taken for antibody levels. Intradermal skin tests with 0·5 μg purified protein derivative of tuberculin (PPD)* and 0·1 ml candida and streptococcal antigens (Bencard) were carried out. The patients were sensitized with 2 mg dinitrochlorobenzene (DNCB) dissolved in two drops of acetone and the area was occluded with plaster. They were then immunized with 0·5 ml tetanus toxoid (Burroughs Wellcome) given intramuscularly, and 0·1 ml Salmonella typhi vaccine (Burroughs Wellcome) given intradermally. On the same day patients were given chloroquine syrup, cough mixture, and prescribed procaine penicillin daily for 5 days. 48 hours later (day 3) skin tests were read as positive or negative, induration of 2 mm or more indicating a positive test. Pyrimethamine was given on day 3 and one week later. 14 days after the start of the investigation children returned for repeat skin tests and a challenge dose of 200 μg DNCB. 2 days later (day 16) the children were weighed, blood was taken for antibody levels, and the skin tests were read.

Laboratory methods. Heterophile antibody levels, antibody levels to tetanus toxoid and to the H and O antigens of Salm. typhi were measured as previously described (Greenwood et al., 1972). Immunoglobulin levels were determined by radial immunodiffusion using monospecific antisera.† Results were recorded in IU. Albumin and transferrin levels were also determined by radial immunodiffusion using a pool of local sera as a standard. Results were recorded as a percentage of this standard. Lymphocytes were purified and cultured as previously described (Greenwood et al., 1972).

Results

Established cellular immune responses. The number of patients and controls with positive skin tests to PPD, candida, and streptococcal

*Central Veterinary Laboratory, Weybridge, Surrey.
†Provided by Dr. D. S. Rowe, WHO International Reference Centre for Immunoglobulins, Lausanne.

antigens is shown in Table I. On day 3, children with measles had significantly less positive tests to candida (P <0·001) and streptococcal antigen (P <0·02) than the controls. No patient with measles reacted to PPD.

After repeat skin testing, read on day 16, the number of reactions in the measles group was comparable to the controls. Among patients with measles the difference in results obtained between day 3 and day 16 was significant for all 3 antigens (Table I).

Induction of cellular immune responses. 31 of the 33 measles patients (94%), previously sensitized with 2 mg DNCB, responded to a challenge of 200 μg DNCB.

The PHA response of lymphocytes from 11 patients with measles was lower than that of the response of 13 healthy controls, but the difference was not statistically significant. On morphological assessment the mean percentage blast cell transformation after stimulation with PHA was 69±13% for the patients with measles and 77±7% for the controls. On scintillation counting the mean value in counts per minute for stimulated cultures less unstimulated cultures was 15,720±14,550 for the measles patients and 22,410±11,600 for the controls. A very low PHA response was shown by lymphocytes from one patient with measles but by none of the controls.

Established humoral responses. The mean heterophile antibody level determined on day 1 of the investigation did not differ significantly between the patients with measles and the controls. Likewise no significant difference was found in the immunoglobulin levels of the two groups on day 1 of the investigation (Table II).

Induction of antibody responses. The antibody response to immunization with Salm. typhi

TABLE I
Number of children with positive skin tests to PPD, candida, and streptococcal antigens

Group	PPD		Candida		Streptococcus	
	Day		Day		Day	
	3	16	3	16	3	16
Measles no. = 33	0	6 P <0·05	6	19 P <0·01	3	14 P <0·01
Controls no. = 34	4	ND	21	ND	13	ND
	NS		P <0·001		P <0·02	

PPD, purified protein derivative of tuberculin; NS, not significant; ND, not done.

TABLE II

Serum immunoglobulin levels (IU/ml) on day 1 of study (mean ± SD)

	IgA	IgG	IgM
Measles no. = 33	59 ± 23	143 ± 49	196 ± 87
Controls no. = 34	56 ± 27	158 ± 63	177 ± 71
	NS	NS	NS

NS, not significant.

vaccine is shown in Table III. Children with measles showed a significantly smaller rise in the titre of antibody to the H and O antigens of *Salm. typhi* than did the controls. 9 of the 33 patients with measles (27%) showed a response to immunization with tetanus vaccine compared with 17 of 34 controls (50%). The difference, however, is not significant (P = 0·05 −0·1).

Nutritional and other effects. There was no significant change in the average weight of the children with measles during the period of the investigation. One child subsequently lost more than 10% of his weight after an attack of diarrhoea and was admitted to hospital. The remaining children made an uneventful recovery.

On day 1 the mean serum albumin level of the patients with measles (95 ± 25%) was significantly lower than that of the control patients (110 ± 25%) (P <0·01). However, no significant difference was found in the mean serum transferrin level of the two groups (120 ± 31% for measles and 132 ± 37% for controls). Among the patients with measles, no significant difference was found between the mean serum albumin or transferrin levels measured on day 16 compared with those obtained on day 1.

The mean Hb level of the children with measles was 10·9 g/100 ml at the start of the study. This had not changed significantly on day 16 (11·0 g/100

TABLE III

Antibody response to immunization with Salm. typhi vaccine

Group	H antigen	O antigen
Measles no. = 33	5·0 ± 2·1	1·5 ± 1·6
Controls no. = 34	6·3 ± 1·3	3·2 ± 1·8
	P <0·01	P <0·001

Note: Results expressed as mean rise in tube titre in doubling dilutions.

ml). The mean leucocyte count for the patients with measles on day 1 was 7617/mm³, 54% of these cells being lymphocytes. No significant change in these values was found on day 16. One patient had hypochromic red cells, none showed macrocytosis or hypersegmentation of the polymorph neutrophil leucocytes.

Discussion

Our findings confirmed that measles causes a temporary suppression of the skin reaction to PPD, candida, and streptococcal antigens. However, when the expression of delayed hypersensitivity was suppressed, our patients could still be sensitized normally to DNCB and their lymphocytes responded to stimulation with PHA. Others have previously found a normal PHA response after vaccination with live measles vaccine (Fireman *et al.*, 1969) and after *in vitro* cultivation of lymphocytes with measles virus (Smithwick and Berkovich, 1966).

The mechanism of this temporary loss of skin reactivity is not clear. Our findings could be explained by a suppressive effect of the measles virus on the production or function of the soluble lymphocyte factors responsible for the final expression of cellular immunity. This type of situation has been described in some patients with chronic mucocutaneous candidiasis who are unable to produce macrophage inhibition factor (Valdimarsson *et al.*, 1970). However, this hypothesis does not explain the finding of Smithwick and Berkovich (1966) that, *in vitro*, measles virus suppresses the response of lymphocytes to tuberculin but not to PHA. Thus, as an alternate explanation, we suggest that the function of thymus-dependent memory cells may be selectively impaired because the measles virus has induced changes in some antigen receptors on their cell surface.

Established humoral immunity was not altered by measles infection. In contrast, the induction of a humoral immune response to the H and O antigens of *Salm. typhi*, and possibly to tetanus toxoid, was deficient. Rinderpest, a virus closely related to measles, has previously been shown to depress the antibody response to chicken erythrocytes in rabbits (Penhale and Pow, 1970). The pathogenesis and pathology of measles and rinderpest are very similar, and it is of interest that latent infections, particularly protozoal, are frequently activated after rinderpest (Curasson, 1932). Suppression of humoral immunity has now been recorded in a number of virus infections of animals and man (Salaman, 1970), but the mechanism of this suppression has not been established.

Impairment of the expression of cellular immunity during measles may explain why conditions such as tuberculosis and moniliasis are sometimes reactivated by this disease. Defects in humoral immunity, together with local epithelial damage, may account for the high incidence of secondary bacterial infection occurring after measles in the tropics. Bronchopneumonia, particularly staphylococcal, is the commonest cause of death (Williams and Osotimehin, 1970). Other pyogenic infections such as otitis media and purulent infections of the eye and skin are also seen frequently in patients with measles.

The aetiology of cancrum oris is unknown, but this condition is frequently preceded by an attack of measles. Vincent's organism can frequently be isolated from the mouth ulcers in this condition. It is possible that measles-induced suppression of the host's immune response allows this or a similar normally harmless organism to become pathogenic.

We have previously shown that most other febrile illnesses do not suppress cellular or humoral immunity in children seen at Zaria (Greenwood et al., 1972). Children with malaria, which suppresses humoral immunity (Greenwood et al., 1972), were excluded at the start of the study and all patients and controls were given antimalarial therapy. None of our patients had clinical signs of severe malnutrition, and laboratory investigations showed a slight lowering of the serum albumin as the only effect of measles on the nutrition of our patients. It thus seems likely that the immunosuppression observed in measles is due to a direct effect of the virus and not one mediated by the production of malnutrition or by the induction of a febrile response.

Severe protein-calorie malnutrition impairs the induction of humoral immunity (Brown and Katz, 1965) and the induction and expression of cellular immunity (Smythe et al., 1971; Geefhuysen et al., 1971), probably by different mechanisms than the measles virus. The effect of the two conditions on the immune system may therefore be synergistic, accounting for the frequent and severe infections which occur in malnourished children with measles.

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